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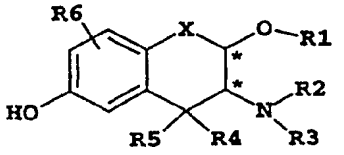
(54) Title: NOVEL OXO–AMINOTETRALIN COMPOUNDS USEFUL IN PAIN MANAGEMENT



(I)

(57) Abstract

The present invention relates to novel oxo–aminotetralin compounds of formula (I), wherein X, R_1, R_2, R_3, R_4, R_5, and R_6 are defined herein. The compounds of formula (I) are useful in pain management.

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NOVEL OXO–AMINOTETRALIN COMPOUNDS USEFUL IN PAIN MANAGEMENT

FIELD OF THE INVENTION

The present invention is related to compounds that exhibit analgesic activity and in particular compounds exhibiting analgesia due to their opioid receptor affinity.

BACKGROUND OF THE INVENTION

Many natural alkaloids and related analogs bind to specific opioid receptors and elicit an analgesic response similar to classic narcotic opiates. Many different types of opioid receptors have been shown to coexist in higher animals. For example, see W. Martin *et al.*, J. Pharmacol. Exp. Ther., 197, p. 517 (1975) ; and J. Lord et al., Nature (London), 257, p.495 (1977). Three different types of opioid receptors have been identified. The first, δ, shows a differentiating affinity for enkephalin-like peptides. The second, μ, shows enhanced selectivity for morphine and other polycyclic alkaloids. The third, κ, exhibits equal affinity for either group of the above ligands and preferential affinity for dynorphin. In general, the μ receptors seem to be more involved with analgesic effects. The δ receptors appear to deal with behavioral effects, although the δ and the κ receptors may also mediate analgesia.

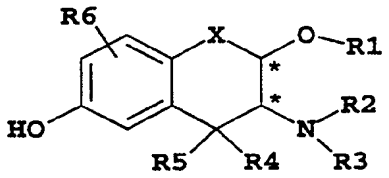
Each opioid receptor, when coupled with an opiate, causes a specific biological response unique to that type of receptor. When an opiate activates more than one receptor, the biological response for each receptor is affected, thereby producing side effects. The less specific and selective an opiate may be, the greater the chance of causing increased side effects by the administration of the opiate.

Opiates can cause serious and potentially fatal side effects. Side effects such as respiratory depression, tolerance, physical dependence capacity, and precipitated withdrawal syndrome are caused by nonspecific interactions with central nervous system receptors. See K. Budd,

In International Encyclopedia of Pharmacology and Therapeutics ; N.E. Williams and H. Wilkinson, Eds., Pergammon : (Oxford), 112, p.51 (1983). It is therefore an object of the present invention to provide compounds having analgesic effects but having as few side-effects as possible.

DESCRIPTION OF THE INVENTION

In one aspect, the present invention provides novel oxo-aminotetralin compounds which are represented by formula (I):



(I)

and pharmaceutically acceptable derivative thereof;

wherein;

X is selected from anyone of

(i) a bond;

(ii) -CR_7R_8- wherein R_7 and R_8 are independently selected from the group consisting of H , OH, halogen, CN, COOH, $CONH_2$, amino, nitro, SH, C_{1-6} alkyl where one or more of the carbon atoms may optionally be substituted by one or more heteroatoms selected from O, S and N, C_{2-6}alkenyl where one or more of the carbon atoms may optionally be substituted by one or more heteroatoms selected from O, S and N, C_{2-6}alkynyl where one or more of the carbon atoms may optionally be substituted by one or more heteroatoms selected from O, S and N; and $COOR_c$ wherein R_c is C_{1-6}alkyl, C_{2-6}alkenyl or C_{2-6}alkynyl; R_7 and R_8 can also be connected to form C_{3-8} cycloalkyl, a C_{3-8} cycloalkenyl or a saturated heterocycle of from 3 to 8 atoms;

R_1 is selected from the group consisting of H, C_{1-12}alkyl where one or more of the carbon atoms may optionally be substituted by one or more heteroatoms selected from O, S and N, C_{2-12}alkenyl where one or more of the carbon atoms may optionally be substituted by one or more heteroatoms selected from O, S and N, C_{2-12}alkynyl where one or more of the carbon atoms may optionally be substituted by one or more heteroatoms selected from O, S and N, C_{6-12} aryl, C_{6-12} aralkyl, C_{6-12} aryloxy, C_{1-12} acyl, heteroaryl having from 6 to 12 atoms, and phosphoryl;

R_2 and R_3 are independently selected from the group consisting of C_{1-6} alkyl where one or more of the carbon atoms may optionally be substituted by one or more heteroatoms selected from O, S and N, C_{2-6}alkenyl where one or more of the carbon atoms may optionally be substituted by one or more heteroatoms selected from O, S and N, C_{2-6}alkynyl where one or more of the carbon atoms may optionally be substituted by one or more heteroatoms selected from O, S and N, C_{6-12} aryl, C_{6-12} aralkyl, heteroaryl having from 6 to 12 atoms, and H; ***or***

R_2 and R_3 may together form a saturated heterocycle of from 3 to 8 atoms;

R_4 and R_5 are independently selected from the group consisting of C_{1-6} alkyl where one or more of the carbon atoms may optionally be substituted by one or more heteroatoms selected from O, S and N, C_{2-6}alkenyl where one or more of the carbon atoms may optionally be substituted by one or more heteroatoms selected from O, S and N, C_{2-6}alkynyl where one or more of the carbon atoms may optionally be substituted by one or more heteroatoms selected from O, S and N, and H;

R_4 **and** R_5 can also be connected to form C_{3-8} cycloalkyl, a C_{3-8} cycloalkenyl or a saturated heterocycle of from 3 to 8 atoms;

R_6 is hydrogen, OH, C_{1-6} alkyl where one or more of the carbon atoms may optionally be substituted by one or more heteroatoms selected from O, S and N, C_{2-6}alkenyl where one or more of the carbon atoms may optionally be substituted by one or more heteroatoms selected from O, S and N, C_{2-6}alkynyl where one or more of the carbon atoms may optionally be substituted by one or more heteroatoms selected from O, S and N, O-C_{1-6} alkyl where one or more of the carbon atoms may optionally be substituted by one or more heteroatoms selected from O, S and N, O-C_{2-6}alkenyl where one or more of the carbon atoms may optionally be substituted by one or more heteroatoms selected from O, S and N, O-C_{2-6}alkynyl where one or more of the carbon atoms may optionally be substituted by one or more heteroatoms selected from O, S and N, halogen, CN, COOH, $CONH_2$, amino, nitro, or SH;

with the provisos that:

1) not both R_4 and R_5 are H; and

2) at least one of R_2 and R_3 is H or C_{1-6} alkyl.

The compounds of the present invention are useful in therapy, in particular as analgesics.

In another aspect, there is provided a method of treating pain in a mammal comprising administering to said mammal an analgesic amount of a compound or composition of the present invention.

Still another aspect of the invention is the use of a compound according to formula (I), for the manufacture of a medicament for the treatment of pain.

In another aspect, there is provided pharmaceutical compositions comprising compounds of the present invention and pharmaceutically acceptable carriers, diluents or adjuvants.

X is preferably -CR_7R_8- wherein R_7 and R_8 are independently selected from the group consisting of OH, halogen, CN, COOH, $CONH_2$, amino, nitro, SH, C_{1-6} alkyl where one or more of the carbon atoms may optionally be substituted by one or more heteroatoms selected from O, S and N, H, and $COOR_c$ wherein R_c is C_{1-6}alkyl; R_7 and R_8 can also be connected to form a C_{3-8} cycloalkyl.

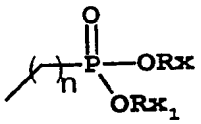
X is more preferably -CR_7R_8- wherein R_7 and R_8 are independently selected from the group consisting of C_{1-6} alkyl, and H.

X is most preferably -CH_2-.

R_1 is preferably selected from the group consisting of H, C_{1-12}alkyl, C_{6-12} aryl, and C_{6-12} aralkyl.

R_1 is more preferably selected from the group consisting of C_{1-6}alkyl, C_{6-12} aryl, and C_{6-12} aralkyl.

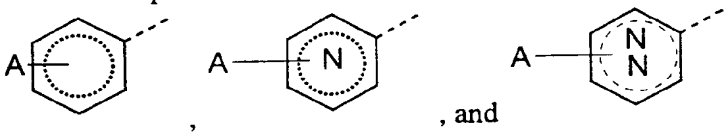
R_1 is most preferably C_{1-6} alkyl.

R_1 can also be  , wherein **n** is an integer between 1 to 5, **Rx** and Rx_1 are independently H, C_{1-6}alkyl, C_{2-6}alkenyl or C_{2-6}alkynyl. More preferably, **n** is 1 or 2 and **Rx** and Rx_1 are C_{1-6}alkyl. Most preferably, **Rx** and Rx_1 are methyl or ethyl.

In an alternative embodiment, R_1 is selected from the group consisting of CH_3, $-(CH_2)_n-CH_3$, and $-(CH_2)_n-O-CH_3$ wherein n is an integer selected between 1 and 5

In an alternative preferred embodiment R_1 is C_{6-12} aryl or heteroaryl having from 6 to 12 atoms.

In a further preferred embodiment, R_1 is selected from the group consisting of

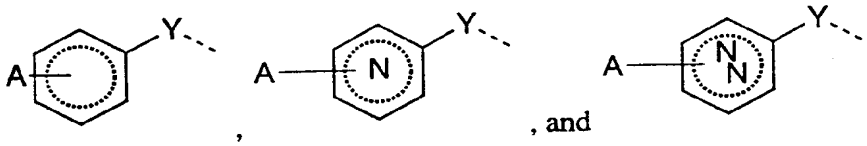


, and

wherein **A** is selected from the group consisting of C_{1-6} alkyl, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, O-C_{1-6} alkyl, O-C_{2-6}alkenyl, O-C_{2-6}alkynyl, , S-C_{1-6} alkyl, S-C_{2-6}alkenyl, S-C_{2-6}alkynyl, N-C_{1-6} alkyl, N-C_{2-6}alkenyl, N-C_{2-6}alkynyl, CF_3, fluoro, chloro, bromo, iodo, OH, SH, CN, nitro, amino, aminoamidino, amidino, guanido, COOH, and $COOR_z$ wherein R_z is C_{1-6}alkyl, C_{2-6}alkenyl or C_{2-6}alkynyl.

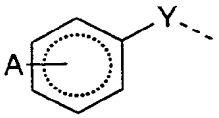
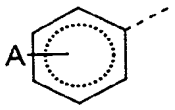
In an alternative embodiment, R_1 is C_{6-12} aralkyl or heteroaryl having from 6 to 12 atoms.

More preferably, R_1 is selected from the group consisting of



, and

wherein **A** is selected from the group consisting of C_{1-6} alkyl, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, O-C_{1-6} alkyl, O-C_{2-6}alkenyl, O-C_{2-6}alkynyl, , S-C_{1-6} alkyl, S-C_{2-6}alkenyl, S-C_{2-6}alkynyl, N-C_{1-6} alkyl, N-C_{2-6}alkenyl, N-C_{2-6}alkynyl, CF_3, fluoro, chloro, bromo, iodo, OH, SH, CN, nitro, amino, aminoamidino, amidino, guanido, COOH, and $COOR_z$ wherein R_z is C_{1-6}alkyl, C_{2-6}alkenyl or C_{2-6}alkynyl and **Y** is $-(CH_2)_m-$ wherein **m** is an integer selected between 1 and 5.

R_1 is preferably  or  wherein **A** and **Y** are as defined above.

A is preferably selected from the group consisting of C_{1-6} alkyl, O-C_{1-6} alkyl, S-C_{1-6} alkyl, OH, nitro, amino, aminoamidino, amidino, guanido, COOH, and $COOR_a$ wherein R_a is C_{1-6}alkyl, C_{2-6}alkenyl or C_{2-6}alkynyl. **A** is more preferably selected from the group consisting of C_{1-6} alkyl, OH, nitro, amino, aminoamidino, amidino, guanido, and COOH. **A** is most preferably selected from the group consisting of amidino, guanido, and OH.

R_2 and R_3 are preferably H.

R_4 and R_5 are preferably C_{1-4} alkyl substituted by a hydroxyl.

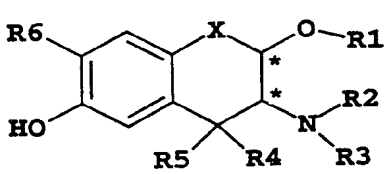
R_4 and R_5 are preferably C_{1-4} alkyl.

In a further preferred embodiment, R_4 and R_5 are independently selected from the group consisting of methyl, ethyl, isopropyl, propyl, butyl, and isobutyl.

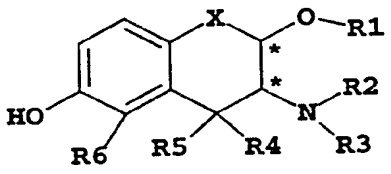
R_4 and R_5 are preferably ethyl.

R_4 and R_5 are preferably methyl.

R_6 can be substituted at any position on the aromatic ring. More preferably R_6 is adjacent to the carbon bearing the OH. In an alternative embodiment, the present invention provides compounds of the formula (II) or (III)



(II)



(III)

and pharmaceutically acceptable derivative;

wherein each of **X**, R_1, R_2, R_3, R_4, R_5, and R_6 are defined above.

R_6 is preferably, H, methyl, halogen or OR_b wherein R_b is C_{1-6}alkyl, C_{2-6}alkenyl or C_{2-6}alkynyl.

R_6 is most preferably H.

The compounds of the present invention contains at least 2 chiral centers which are marked by an asterik (*) on the general formula (I). The compounds of formula (I) thus exist in the form of different geometric(i.e. *trans* and *cis*) and optical isomers (i.e. (+) or (-) enantiomers). When there is 2 chiral centers at the position marked by the asteriks, the compounds may be therefore be in the form of *cis* isomers or *trans* isomers. Each *cis* or *trans* isomers also exists as a (+) and (-) enantiomer. All such isomers, enantiomers and mixtures thereof including racemic mixtures are included within the scope of the invention.

Preferably the compounds of the present invention are in the form of the *trans* isomers (between the centers marked by an asteriks on the general formula (I)). More preferably the compounds of the present invention are present in the form of *trans*- (+) enantiomers and *trans* (-) enantiomers.

Preferred compounds of the invention include:
Trans-7-Amino-6-ethoxy-8,8-diethyl-5,6,7,8-tetrahydro-naphthalen-2-ol **(compound#1)**;Trans-7-Amino-6-methoxy-8,8-dimethyl-5,6,7,8-tetrahydro-naphthalen-2-ol **(compound#2)**;
Trans-7-Amino-8,8-dimethyl-6-phenoxy-5,6,7,8-tetrahydro-naphthalen-2-ol **(compound#3)**;
Trans-7-Amino-6-isopropoxy-8,8-dimethyl-5,6,7,8-tetrahydro-naphthalen-2-ol **(compound#4)**;
Trans-7-Amino-8,8-dimethyl-6-propoxy-5,6,7,8-tetrahydro-naphthalen-2-ol **(compound#5)**;
Trans-7-Amino-8,8-dimethyl-6-(2-phenoxy-ethoxy)-5,6,7,8-tetrahydro-naphthalen-2-ol **(compound#6)**;
Trans-7-Amino-6-ethoxy-8,8-dimethyl-5,6,7,8-tetrahydro-naphthalen-2-ol **(compound#7)**;

Trans-7-Amino-8,8-diethyl-6-(2-methoxy-ethoxy)-5,6,7,8-tetrahydro-naphthalen-2-ol (**compound#8**);

Trans-7-Amino-8,8-diethyl-6-methoxy-5,6,7,8-tetrahydro-naphthalen-2-ol (**compound#9**);

Trans-7-Amino-8,8-diethyl-6-(2-hydroxy-ethoxy)-5,6,7,8-tetrahydro-naphthalen-2-ol (**compound#10**);

Trans-7-Amino-8,8-spiropentanyl-6-methoxy-5,6,7,8-tetrahydro-naphthalen-2-ol (**compound#11**);

Trans-7-Amino-6-methoxy-8,8-dipropyl-5,6,7,8-tetrahydro-naphthalen-2-ol **(compound#12)**;

Trans-7-Amino-6-ethoxy-8,8-dipropyl-5,6,7,8-tetrahydro-naphthalen-2-ol **(compound#13)**;

Trans-7-Amino-6-(2-phenoxy-ethoxy)-8,8-dipropyl-5,6,7,8-tetrahydro-naphthalen-2-ol **(compound#14)**;

Trans-3-Amino-4,4-diethyl-1,2,3,4-tetrahydro-naphthalene-2,6-diol **(compound#15)**

(-)Trans-3-Ethoxy-1,1-diethyl-7-hydroxy-1,2,3,4-tetrahydro-naphthalen-2-yl-ammonium chloride **(compound #16)**;

(+)Trans-3-Ethoxy-1,1-diethyl-7-hydroxy-1,2,3,4-tetrahydro-naphthalen-2-yl-ammonium chloride **(compound #17)**;

1,1-diethyl-7-hydroxy-3-trans-(3-hydroxy-propoxy)-1,2,3,4-tetrahydro-naphthalen-2-yl-ammonium; chloride **(compound#18);**

7-Amino-6-(2-amino-ethoxy)-8,8-diethyl-5,6,7,8-tetrahydro-naphthalen-2- ol; BIS-trifluoroacetic acid salt **(compound#19);**

3-(3-Amino-4,4-diethyl-6-hydroxy-1,2,3,4-tetrahydro-naphthalen-2-yloxy)-propionic acid; trifluoroacetic acid salt **(compound#20);**

and pharmaceutically acceptable derivative thereof; wherein said compound in the form of the (+) enantiomer, the (-) enantiomer and mixture of the (+) and (-) enantiomer including racemic mixture

More Preferred compounds of this invention are selected from the group consisting of:

compound#1, compound#2, compound#3, compound#4, compound#5, compound#6, compound#7, compound#8, compound#9, compound#12, compound#16, compound#17, compound#18 and compound#19.

Most preferred compounds of the present invention are selected from the group consisting of **compound#1, compound#2, compound#5, compound#8, compound#9, compound#16, compound#17, compound#18 and compound#19.**

As used in the present application the term "pain" represents "an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage. The term "pain" also includes "acute pain" and chronic pain.

Acute pain is usually immediate and of a short duration. Acute pain can be present further to an injury, short-term illness, or surgical/medical procedure.

Examples of acute pain include a burn, a fracture, an overused muscle, or pain after surgery. Cancer pain may be long-lasting but acute due to ongoing tissue damage.

Some chronic pain is due to damage or injury to nerve fibers themselves (neuropathic pain).

Chronic pain can result from diseases, such as shingles and diabetes, or from trauma, surgery or amputation (phantom pain). It can also occur without a known injury or disease.

The present invention is directed to the treatment of all type of pain, including acute and chronic pain.

As used in this application, the term **"alkyl"** represents an unsubstituted or substituted (by a halogen, nitro, aminoamidino, amidino, guanido, $CONH_2$, COOH, O-C_{1-6} alkyl, O-C_{2-6} alkenyl, O-C_{2-6} alkynyl, amino, hydroxyl or **COOQ,** wherein **Q** is C_{1-6} alkyl, C_{2-6} alkenyl, a C_{2-6} alkynyl) straight chain, branched chain, or cyclic hydrocarbon moiety (e.g. isopropyl, ethyl, flurohexyl or cyclopropyl). The term alkyl is also meant to include alkyls in which one or more hydrogen atoms is replaced by an halogen, more preferably, the halogen is fluoro (e.g., CF_3-, or CF_3CH_2-).

The term **"saturated heterocycle"** represents a carbocyclic ring in which one or more of the from 3 to 8 atoms of the ring are elements other than carbon, such as N, S and O;

The term **"aryl"** represents an aromatic ring having from 6 to 12 carbon atoms, which may be substituted by a C_{1-6} alkyl, C_{2-6} alkenyl, a C_{2-6} alkynyl, halogen, nitro, aminoamidino, amidino, guanido, $CONH_2$, COOH, O-C_{1-6} alkyl, O-C_{2-6} alkenyl, O-C_{2-6} alkynyl, amino, hydroxyl or **COOQ,** wherein **Q** is C_{1-6} alkyl, C_{2-6} alkenyl, a C_{2-6} alkynyl, such as phenyl and naphthyl.

The term **"aralkyl"** represents an aryl group attached to the adjacent atom by a C_{1-6}alkyl, C_{1-6}alkenyl, or C_{1-6}alkynyl(e.g., benzyl).

The term **"aryloxy"** represents an aryl or aralkyl moiety covalently bonded through an oxygen atom (e.g., phenoxy).

The term **"heteroaryl"** represents an aromatic ring in which one or more of the from 6 to 12 atoms in the ring are elements other than carbon, such as O, N, and S (e.g pyridine, isoquinoline, or benzothiophene).

The term **"acyl"** refers to a radical derived from a carboxylic acid, substituted (by halogen(F, Cl, Br, I), C_{6-20} aryl or C_{1-6} alkyl) or unsubstituted, by replacement of the OH group. Like the acid to which it is related, an acyl radical may be aliphatic or aromatic, substituted (by halogen, C_{1-5} alkoxyalkyl, nitro or OH) or unsubstituted, and whatever the structure of the rest of the molecule may be, the properties of the functional group remain essentially the same (e.g., acetyl, propionyl, isobutanoyl, pivaloyl, hexanoyl, trifluoroacetyl, chloroacetyl, and cyclohexanoyl).

The term **"phosphoryl"** represents a radical derived from a phosphono moeity in which the hydrogen atom of at least one of the -OH can be replaced by C_{1-6} alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6}heteroalkyl, C_{6-12} aryl, C_{6-12} aralkyl, and C_{6-12} heteroaryl(e.g., diethoxyphosphorylmethyl).

The term **"halogen"** encompasses chloro, fluoro, bromo and iodo.

When there is a sulfur atom present, the sulfur atom can be at different oxydation level, S, SO, or SO_2. All such oxydation level are within the scope of the present invention.

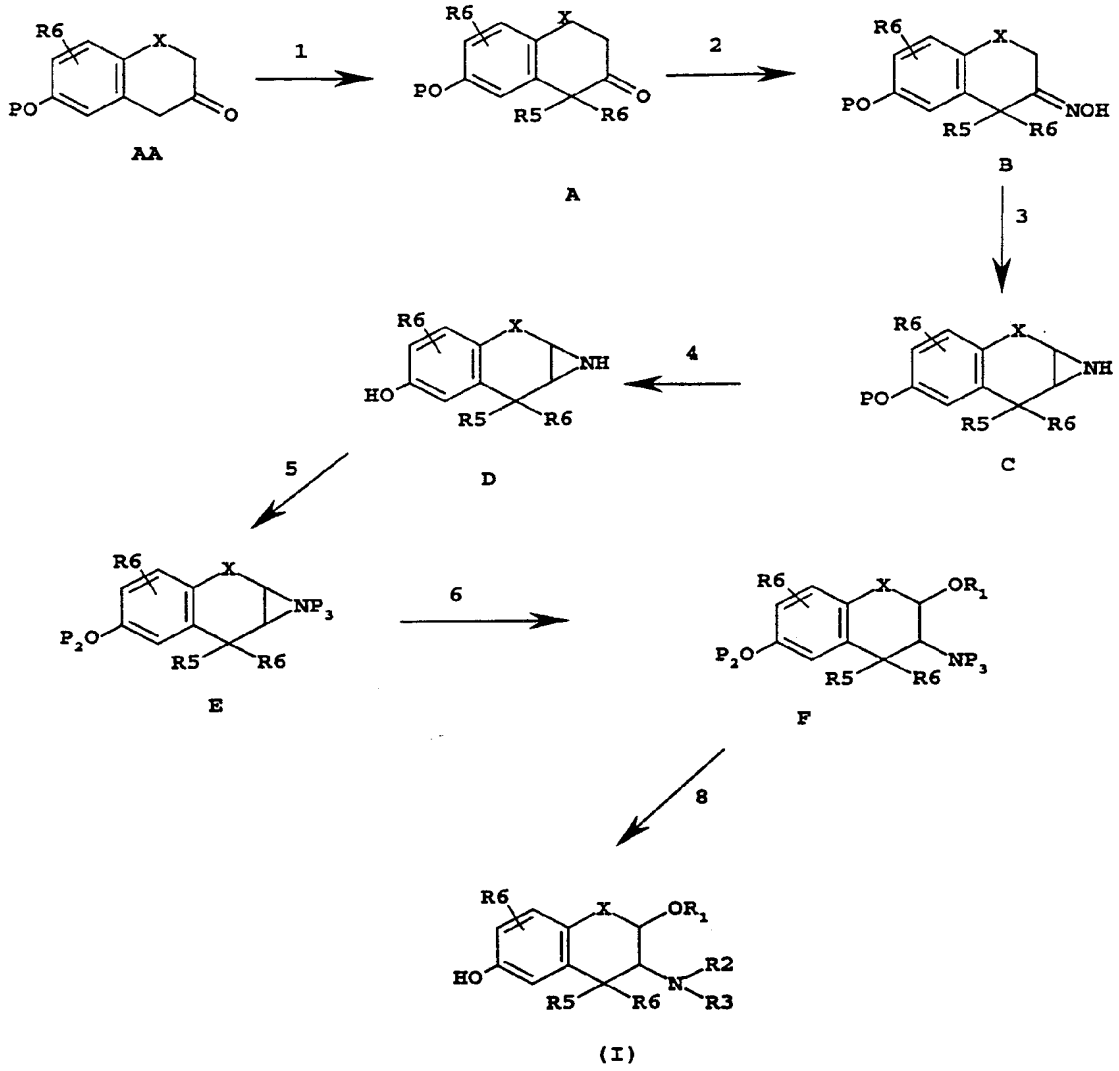
In the present application the following abbreviations are used:

AcOEt	ethyl acetate
Boc	t-butyloxycarbonyl
DMAP	4-dimethylaminopyridine
DME	ethylene glycol dimethylether
DMF	dimethylformamide
Et_2O	ether
Hex	hexane
HPLC	high performance liquid chromatography

LAH	lithium aluminium hydride
LHMDS	lithium bis(trimethylsilyl)amide
NHMDS	sodium bis(trimethylsilyl)amide
Ph	phenyl
PPTS	pyridium *p*-toluenesulfonate
PTSA	*p*-toluenesulfonic acid
r.t.	room temperature
sat.	saturated
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TLC	thin layer chromatography

In yet another aspect of the invention, there is provided a process for preparing compounds of formula (I). The process is described in scheme 1 wherein each of **X**, $\mathbf{R_1}$, $\mathbf{R_2}$, $\mathbf{R_3}$, $\mathbf{R_4}$, $\mathbf{R_5}$ and $\mathbf{R_6}$ are as defined above and **P**, **P1**, **P2**, and **P3** are protecting groups.

SCHEME 1



Step 1

The starting ketone **AA** was dissolved in a suitable solvent such as DMF, acetonitrile, THF, DME and was treated with sodium hydride or any other base such as potassium t-butoxide, sodium bis(trimethylsilyl)amide. The resulting mixture was then treated with ethyl iodide or any other alkyl halide such as methyl iodide, allyl bromide, diiodobutane to produce the compound **A**.

Step 2

The compound **A** was dissolved in a suitable solvent such as pyridine, DMF, ethanol and was treated with hydroxylamine hydrochloride or any other hydroxylamine salt such as hydroxylamine sulfate, hydroxylamine bromide to produce the compound **B**.

Step 3

The compound **B** was dissolved in a suitable solvent as THF, dioxane, DME, and was treated with LAH or any other reducing agent such as red-Al in presence of diethylamine or any other amine such as methylbutylamine, dipropylamine. The mixture was then heated to 50°C or at any higher temperature to produce the compound **C**.

Step 4

The compound **C** in was dissolved in a suitable solvent as dichloromethane (CH_2Cl_2) or in any other solvent such as dichloroethane, and was treated with BBr_3 or any other demethylating agent such as BCl_3, HBr, to produce the compound **D**.

Step 5

The amino or hydroxyl groups of the compound **D** were protected with Boc or with any other protecting, to produce the compound **E**. Protective groups are described in Protective Groups in Organic Synthesis, 2nd ed., Greene and Wuts, John Wiley & Sons, New York, 1991 which is herein incorparated by reference.

Step 6

The compound **E** was dissolved in a suitable solvent such as ethanol or in any other alcohol such as methanol, propanol, butanol and was treated with pyridinium p-toluenesulfonate (PPTS) or any other acid or Lewis acid such as HCl, $BF_3.OEt_2$, PTSA, to produce the compound **F**. Alternatively, a non alcoholic solvent can be used in combination with an appropriate amount of an alcohol and a suitable Lewis acid such as ytterbium triflate see for example *Tetrahedron Letters*, Vol. 37, No.43, pp7717-7720, 1996 which is herein incorparated by reference.

Step 7

The protecting groups of the compound **F** were removed under appropriate conditions e.g. with TFA or with any other acid such as HCl, PTSA, to produce the compound **I.**

It will be appreciated that certain substituents require protection during the course of the synthesis and subsequent deprotection. For example, it may be necessary to protect an hydroxyl group by converion to an alkoxy or an ester and subsequently deprotected. Protective groups for other substituents are described in Protective Groups in Organic Synthesis, 2nd ed., Greene and Wuts, John Wiley & Sons, New York, 1991.

In another aspect, there is provided a method of agonizing or activating opioid receptors in a mammal comprising administering to said mammal an opioid receptor agonizing or activating amount of a compound or composition of the invention.

There is also provided a pharmaceutically acceptable compositions comprising compounds of the present invention and derivatives thereof, in combination with pharmaceutically acceptable carriers diluents or adjuvants. By "derivative" is meant any pharmaceutically acceptable salt, ester, or salt of such ester, of compounds of formula (I) or (II) or any other

compound which, upon administration to the recipient, is capable of providing (directly or indirectly) compounds of formula (I) or (II) or an active metabolite or residue thereof.

The present invention also provides pharmaceutical compositions which comprise a pharmaceutically effective amount of a compound of the invention, or pharmaceutically acceptable salts thereof, and preferably, a pharmaceutically acceptable carrier, diluent or adjuvant. The term "pharmaceutically effective amount" is the amount of compound required upon administration to a mammal in order to induce analgesia. Also, the term "opioid receptor agonizing amount" refers to the amount of compound administered to a mammal necessary to bind and/or activate opioid receptors in vivo.

Therapeutic methods of this invention comprise the step of treating patients in a pharmaceutically acceptable manner with those compounds or compositions. Such compositions may be in the form of tablets, capsules, caplets, powders, granules, lozenges, suppositories, reconstitutable powders, or liquid preparations, such as oral or sterile parenteral solutions or suspensions.

In order to obtain consistency of administration, it is preferred that a composition of the invention is in the form of a unit dose. The unit dose presentation forms for oral administration may be tablets and capsules and may contain conventional excipients. For example, binding agents, such as acacia, gelatin, sorbitol, or polyvinylpyrolidone; fillers, such as lactose, sugar, maize-starch, calcium phosphate, sorbitol or glycine; tabletting lubricants such as magnesium stearate; disintegrants, such as starch, polyvinylpyrrolidone, sodium starch glycollate or microcrystalline cellulose; or pharmaceutically acceptable wetting agents such as sodium lauryl sulphate.

The compounds may be administered orally in the form of tablets, capsules, or granules containing suitable excipients such as starch, lactose, white sugar and the like. The compounds may be administered orally in the form of solutions which may contain coloring and/or flavoring agents. The compounds may also be administered sublingually in the form of tracheas or lozenges in which each active ingredient is mixed with sugar or corn syrups, flavoring agents and dyes, and then dehydrated sufficiently to make the mixture suitable for pressing into solid form.

The solid oral compositions may be prepared by conventional methods of blending, filling, tableting, or the like. Repeated blending operations may be used to distribute the active agent throughout those compositions employing large quantities of fillers. Such operations are, of course, conventional in the art. The tablets may be coated according to methods well known in normal pharmaceutical practice, in particular with an enteric coating.

Liquid oral preparations may be in the form of emulsions, syrups, or elixirs, or may be presented as a dry product for reconstitution with water or other suitable vehicle before use. Such liquid preparations may or may not contain conventional additives. For example suspending agents, such as sorbitol, syrup, methyl cellulose, gelatin, hydroxyethylcellulose, carboxymethylcellulose, aluminum stearate gel, or hydrogenated edible fats; emulsifying agents, such as sorbitan monooleate or acaci; non-aqueous vehicles (which may include edible oils), such as almond oil, fractionated coconut oil, oily esters selected from the group consisting of glycerine, propylene glycol, ethylene glycol, and ethyl alcohol; preservatives, for instance methyl para-hydroxybenzoate, ethyl para-hydroxybenzoate, n-propyl parahydroxybenzoate, or n-butyl parahydroxybenzoate of sorbic acid; and, if desired, conventional flavoring or coloring agents.

The compounds may be injected parenterally; this being intramuscularly, intravenously, or subcutaneously. For parenteral administration, the compound may be used in the form of sterile solutions containing other solutes, for example, sufficient saline or glucose to make

the solution isotonic. For parenteral administration, fluid unit dosage forms may be prepared by utilizing the compound and a sterile vehicle, and, depending on the concentration employed, may be either suspended or dissolved in the vehicle. Once in solution, the compound may be injected and filter sterilized before filling a suitable vial or ampoule and subsequently sealing the carrier or storage package. Adjuvants, such as a local anesthetic, a preservative or a buffering agent, may be dissolved in the vehicle prior to use. Stability of the pharmaceutical composition may be enhanced by freezing the composition after filling the vial and removing the water under vacuum, (e.g., freeze drying the composition). Parenteral suspensions may be prepared in substantially the same manner, except that the compound should be suspended in the vehicle rather than being dissolved, and, further, sterilization is not achievable by filtration. The compound may be sterilized, however, by exposing it to ethylene oxide before suspending it in the sterile vehicle. A surfactant or wetting solution may be advantageously included in the composition to facilitate uniform distribution of the compound.

The pharmaceutical compositions of this invention comprise a pharmaceutically effective amount of a compound of this invention and a pharmaceutically acceptable carrier. Typically, they contain from about 0.01% to about 99% by weight, preferably from about 10% to about 60% by weight, of a compound of this invention, depending on which method of administration is employed.

The compounds of the present invention can be administered in combination with one or more further therapeutic agents. Preferably, the one or more further therapeutic agent is selected from the group consisting of nonsteroidal anti-inflammatory drugs (NSAIDs), acetaminophen, narcotics, antidepressants, anticonvulsants, corticosteroid, tramadol, sumatriptan, and capsaicin.

Without limitations, NSAIDs include aspirin (Anacin, Bayer, Bufferin), ibuprofen (Motrin, Advil, Nuprin), naproxen sodium (Aleve) and ketoprofen (Orudis KT)

Without limitations, narcotics include drugs derived from opium (opiates), such as morphine and codeine, and synthetic narcotics (opioids), such as oxycodone, methadone and meperidine (Demerol).

Without limitations, antidepressants include amitriptyline (Elavil), trazodone (Desyrel) and imipramine (Tofranil) may be used with other analgesics. These drugs are especially useful for neuropathic, head and cancer pain.

Without limitations, anticonvulsants include drugs developed for epilepsy, these drugs, such as phonation (Dilantin) and carbamazepine (Tegretol), can also help control chronic nerve pain.

Tramadol (Ultram) is a synthetic analgesic used primarily for chronic pain, but is also prescribed for acute pain.

Sumatriptan (Imitrex),may reduce pain from migraine headache by constricting blood vessels.

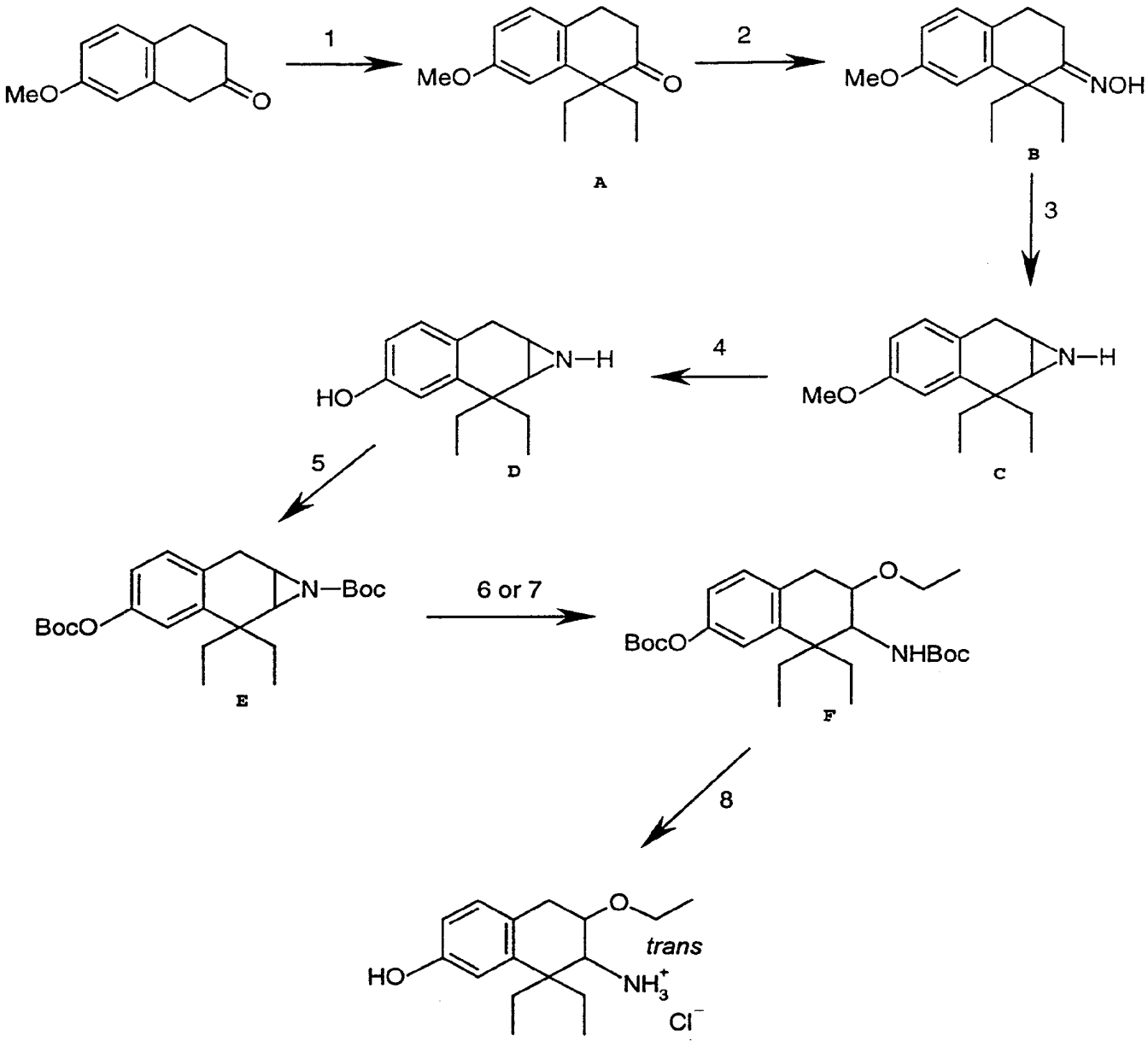
Capsaicin (Zostrix), a topical cream made from an extract of red peppers, can help relieve skin sensitivity resulting from shingles. Capsaicin can also be used to treat pain from arthritis, cluster headaches, diabetic neuropathy and pain after mastectomy.

In another aspect of the invention, compounds may be used to identify opioid receptors from non-opioid receptors. For such use, compounds of the invention are radiolabeled e.g. by incorporating ^{3}H or ^{14}C within its structure or by conjugation to ^{125}I. Such radiolabeled forms can be used directly to identify the presence of opioid receptors and in particular μ opioid receptors in a receptor population. This can be achieved by incubating membrane preparations with a radiolabeled compound of the invention. The presence and or amount of opioid receptors in the preparation is determined from the difference in membrane-bound radioactivity against a control preparation devoid of opioid receptors.

Furthermore, radiolabeled forms of the present compounds can be exploited to screen for more potent opioid ligands, by determining the ability of the test ligand to displace the radiolabeled compound of the present invention.

To further assist in understanding the present invention, the following non-limiting examples are provided. Certain abbreviations are used throughout the examples and can be found in the Aldrich Chemical Company and Bachem catalogues.

EXAMPLE 1



compound # 1

EXAMPLE 1

Synthesis of *trans*-7-Amino-8,8-diethyl-6-methylsulfanyl-5,6,7,8-dihydro-naphthalen-2-ol hydrochloride

Step 1 : 1,1-Diethyl-7-methoxy-3,4-dihydro-1H-naphthalen-2-one (A)

To a solution of 7-methoxy-2-tetralone(4.26 g, 24.18 mmol) in DMF (100 mL) at 0° C was 1 eq of sodium hydride (60% in oil) (1g, 41.6 mmol). After 30 minutes, 1.25 eq of iodoethane was added (2.5 mL, 30.2 mmol), then after 30 min, the other equivalent of sodium hydride (1g), after 30 min the iodoethane was added (2.5 mL, 30.2 mmol). The resulting purpule solution was stirred for 1h at 0°C then stirred for over night at r.t. The mixtutre was quenched with water, then diluted with ether. The organic layer was then washed with H2O, brine, dried over MgSO4, filtered then evaporated. The residue was purified by a flash chromatography (5%AcOEt/ Hex) (4.40g, 78%).

1H NMR (CDCl3) : 7.12 (1H, d, J=8.0Hz), 6.78 (2H, m), 3.84 (3H, s), 2.97 (2H, t, J=6.0 Hz), 2.6 (2H, t, J=6.0 Hz), 2.10 (2H, m), 1.71 (2H, m), 0.63 (6H, t, J=7.5 Hz).

Step 2 : 1,1-Diethyl-7-methoxy-3,4-dihydro-1H-naphthalen-2-one oxime (B)

1,1-Diethyl-7-methoxy-3,4-dihydro-1H-naphthalen-2-one (4.40g, 18.96 mmol) in dry pyridine (20 mL) with the hydroxylamine hydrochloride salt (10.54 g, 151.7 mmol) was heated to 80 °C for one day. The mixture was cooled down to r.t., then the pyridine was removed under vaccum. The green gum was dissolved with AcOEt, washed with H2O, HCl 10%, H2O, brine , dried over MgSO4 and filtered through a small silica pad. The crude compound was used without any other purification (4.69g, 100%).

1H NMR (CDCl3) : 7.94 (1H, s), 7.06 (1H, d, J=8 Hz), 6.84 (1H, d, J=2.5 Hz), 6.73 (1H, dd, J=2.5 and 8 Hz), 3.83 (3H, s), 2.80-2.75 (4H, m), 2.08 (2H, m), 1.85 (2H, m), 0.68 (6H, t, J=7.5 Hz).

Step 3 : 7,7-Diethyl-5-methoxy-1a,2,7,7a-tetrahydro-1H-1-aza-cyclopropa[b]naphthalene (C)

To a solution of 1,1-Diethyl-7-methoxy-3,4-dihydro-1H-naphthalen-2-one oxime (4.68g, 18.96 mmol) in dry THF (100 mL) at 0°C was added the diethylamine (4.9 mL, 47.4 mmol) and the LAH (95% powder) (2.16g, 56.9 mmol). The mixture was stirred at 0° C for 15 min then heated to reflux for 3h. The gray solution was cooled down to 0°C , quenched with brine and diluted with AcOEt. The organic layer was decanted, washed with H2O (2x), brine, dried over MgSO4, filtered then evaporated. The residu was purified by a flash chromatography (3% MeOH/ CH2Cl2) (3.889 g, 89%).

1H NMR (CDCl3) : 6.99 (1H, d, J=8 Hz), 6.76 (2H, m), 3.13 (2H, m), 2.40 (1H, bs), 2.10-2.05 (2H, m), 1.84 (1H, m), 1.62 (4H, m), 1.02 (3H, t, J=7.5 Hz), 0.75 (3H, t, J=7.5Hz).

Step 4 : 7,7-Diethyl-1a,2,7,7a-tetrahydro-1H-1-aza-cyclopropa[b]naphthalen-5-ol(D)

To a solution of 7,7-Diethyl-5-methoxy-1a,2,7,7a-tetrahydro-1H-1-aza-cyclopropa[b]naphthalene(3.889g, 16.81 mmol) in CH2Cl2 (170 mL) at -78°C was added the BBr3 (1M in CH2Cl2) (33.6 mL, 33.62 mmol). The mixture was kept at -78°C for 30 min then to 0°C for 1.5h. The mixture was quenched by NaHCO3, diluted with AcOEt. The organic layer was washed with H2O, brine, dried over MgSO4, filtered then evaporated. The residu was purified by a flash chromatography (3% MeOH /CH2Cl2) (2.917g, 80%).

1H NMR (CDCl3) : 6.93 (1H, d, J=8.0 Hz), 6.68 (1H, d, J=2.5 Hz), 6.64 (1H, dd, J=8 and 2.5 Hz), 3.12 (2H, m), 2.42 (1H, bs), 2.14 (1H, bs), 2.04 (1H, m), 1.82 (1H, m), 1.65 (4H, m), 1.02 (3H, t, J=7.5 Hz), 0.75 (3H, t, J=7.5Hz).

Step 5 : 5-tert-Butoxycarbonyloxy-7,7-diethyl-1a,2,7,7a-tetrahydro-1-aza-cyclopropa[b]naphthalene-1-carboxylic acid tert-butyl ester (E)

To a solution of 7,7-Diethyl-1a,2,7,7a-tetrahydro-1H-1-aza-cyclopropa[b]naphthalen-5-ol (1.5g, 6.90 mmol) in CH2Cl2 (30 mL) at r.t was added the (Boc)2O (3.77g, 17.26 mmol) , the triethylamine (3.85 mL, 27.6 mmol) and DMAP (cat). The mixture was strirred at r.t for over night. The mixture was quenched by NH4Cl, diluted with AcOEt. The organic layer was washed with H2O, brine, dried over MgSO4, filtered then evaporated. The residu was purified by a flash chromatography (5% to 25% AcOEt/Hex) (2.44g, 84%).
1H NMR (CDCl3) : 7.05-6.95 (3H, m), 3.29 (1H, d, J=17 Hz), 3.04 (1H, dd, J=2Hz and 17Hz), 2.94 (1H, m), 2.67 (1H, d, J=6.5 Hz), 2.05-1.95 (2H, m), 1.65-1.50 (11H, m), 1.43 (9H, s), 1.11 (3H, t, J=7.5 Hz), 0.72 (3H, t, J=7.5 Hz).

Step 6 : Carbonic acid 7-tert-butoxycarbonylamino-trans-6-ethoxy-8,8-diethyl-5,6,7,8-tetrahydro-naphthalen-2-yl ester tert-butyl ester (F)

5-tert-Butoxycarbonyloxy-7,7-diethyl-1a,2,7,7a-tetrahydro-1-aza-cyclopropa[b]naphthalene-1-carboxylic acid tert-butyl ester (224.0mg ; 0.54mmol) placed under Argon at room temperature was dissolved in anhydrous ethanol (8.0 mL). To this solution was added a catalytic amount of pyridinium p-toluene sulfonate. The reaction mixture was stirred overnight. The next day, the reaction mixture was poured into an aqueous solution of sodium bicarbonate and it was extracted using dichloromethane. The combined organic layers were dried over sodium sulfate, filtered , and the solvent was removed. The crude was purified by flash chromatography using ; hexanes : ethyl acetate (9 :1) then (8 :2) as the eluent. The isolated product is a solid (129mg, 55%).

Step 7 : Carbonic acid 7-tert-butoxycarbonylamino-trans-6-ethoxy-8,8-diethyl-5,6,7,8-tetrahydro-naphthalen-2-yl ester tert-butyl ester

5-tert-Butoxycarbonyloxy-7,7-diethyl-1a,2,7,7a-tetrahydro-1-aza-cyclopropa[b]naphthalene-1-carboxylic acid tert-butyl ester (346.0mg ; 0.83mmol) placed under Nitrogen was dissolved using anhydrous chloroform (15.0mL) followed by 0.5 equivalents of Ytterbium trifluoromethanesulfonate (257.0 mg ;0.42mmol) were then added. The reaction mixture was allowed to stir at room temperature overnight. The next day, it was poured into an aqueous solution of sodium bicarbonate and extracted using dichloromethane. The combined organic layers were dried over magnesium sulfate, filtered , and the solvent was removed by vacuo. The crude was purified by flash chromatography using ; hexanes : ethyl acetate (9 :1) then (8 :2) as the eluent. The isolated product is a solid (275mg, 71%).

1H NMR (400MHz) (CDCl3; d; ppm): 7.06 (1H, d, J=8.3Hz), 6.93-6.99 (2H, m). 4.33 (1H, d, J=10.4Hz) ; 4.06 (1H, dd, J1=J2=10.0Hz) ; 3.72 (1H, m) ; 3.64 (1H, m) ; 3.54 (1H, m), 3.22 (1H, dd, J1=6.0Hz, J2=16.2Hz), 2.79 (1H, dd, J1=9.5Hz, J2=16.0Hz), 1.72 (3H, m), 1.51 (1H, m), 1.55 (9H, s), 1.47 (9H, s), 1.22 (3H, t, J=7.0Hz) ; 0.74 (3H, t, J=7.5Hz) ; 0.69 (3H, t, J=7.3Hz).

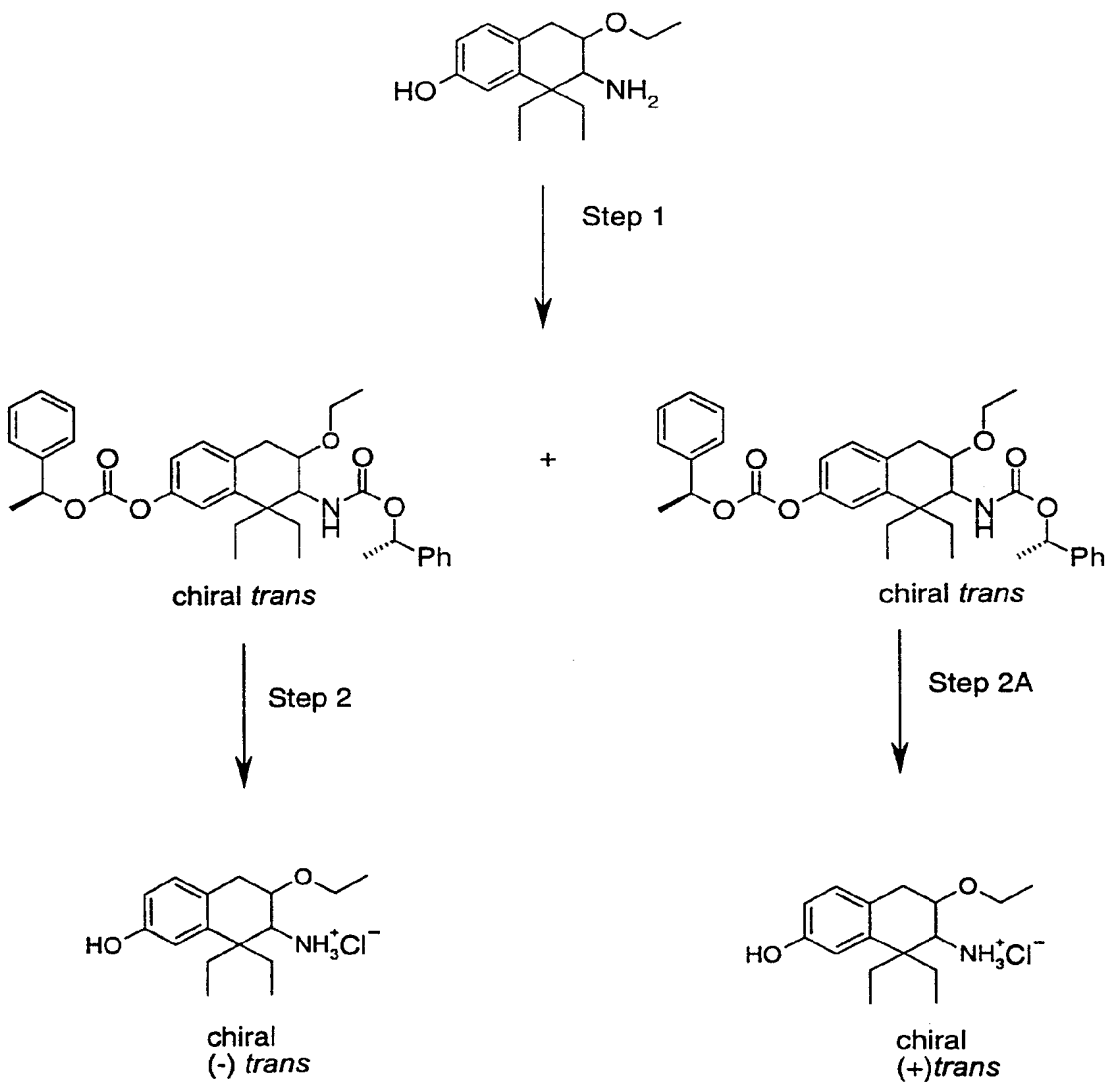
Step 8: Trans-3-Ethoxy-1,1-diethyl-7-hydroxy-1,2,3,4-tetrahydro-naphthalen-2-yl-ammonium chloride (compound #1)

Carbonic acid 7-tert-butoxycarbonylamino-trans-6-ethoxy-8,8-diethyl-5,6,7,8-tetrahydro-naphthalen-2-yl ester tert-butyl ester (200mg ; 0.43mmol) placed under nitrogen at room temperature was dissolved in tetrahydrofuran (5.0mL) and trifluoroacetic acid (3.0mL) was then added and the reaction mixture was stirred for about an hour. The solvents were then evaporated by vacuo and a solution of hydrochloric acid in ether (1.0M) (50mL) was then added. The reaction mixture thus obtained was then stirred for another hour. The solvents

were removed by vacuo and the isolated solid washed several times with ether than dichloromethane. The isolated product is a yellow powder (145mg, >99%).

1H NMR (400MHz) (CD3OD; d; ppm): 6.98 (1H, d, J=8.9Hz), 6.68 (2H, m). 3.96 (1H, m), 3.87 (1H, m), 3.56 (1H, m), 3.39 (2H, m), 2.57 (1H, dd, J1=10.0Hz, J2=15.5Hz), 2.07 (1H, m), 1.73 (1H, m), 1.66 (2H, m), 1.30 (3H, t, J=7.0Hz) 0.80 (3H, t, J=7.4Hz), 0.70 (3H, t, J=7.3Hz).

EXAMPLE 2



Step 1

Trans-7-Amino-6-ethoxy-8,8-diethyl-5,6,7,8-tetrahydro-naphthalen-2-ol (231mg ; 0.88mmol) is placed under nitrogen at room temperature and dissolved with anhydrous acetonitrile (20 mL). Triethylamine 0.25mL (1.75mmol) and the chiral auxiliary reagent 504mg (1.75mmol) are then added. The reaction mixture thus obtained was heated overnight at reflux. The following day, the reaction mixture is cooled back to room temperature and it is then poured into an aqueous solution of sodium bicarbonate and extracted using dichloromethane. The combined organic layers were washed with 0.1N HCl, brine, and were then dried over sodium sulfate. After filtration, the solvent was removed by vacuo. The crude was purified by flash chromatography using ; hexanes : ethyl acetate (9 :1) then (8 :2) as the eluent. The isolated products are a colorless oils (72%).

(less polar isomer): 1H NMR (400MHz) (CDCl3; d; ppm): 7.41 (10H, m) ; 7.03 (1H, m) ; 6.94 (2H, m) ; 5.84 (2H, m) ; 4.54 (1H, d) ; 4.10 (1H, m) ; 3.61 (2H, m) ; 3.39 (1H, m) ; 3.19 (1H, m) ; 2.72 (1H, m) ; 1.71 (2H, m) ; 1.64 (3H, d) ; 1.50-1.62 (2H, m) ; 1.57 (3H, d) ; 0.98 (3H, t, J=7.0Hz) ; 0.72 (6H, 2t).

(more polar isomer): 1H NMR (400MHz) (CDCl3; d; ppm): 7.37 (10H, m) ; 7.03 (1H, m) ; 6.95 (2H, m) ; 5.82 (2H, m) ; 4.51 (1H, d) ; 4.10 (1H, m) ; 3.71 (2H, m) ; 3.55 (1H, m) ; 3.23 (1H, dd) ; 2.80 (1H, dd) ; 1.40-1.78 (4H, m) ; 1.67 (3H, d) ; 1.56 (3H, d) ; 1.22 (3H, t) ; 0.68 (6H, 2t).

Step 2

(-)Trans-3-Ethoxy-1,1-diethyl-7-hydroxy-1,2,3,4-tetrahydro-naphthalen-2-yl-ammonium chloride (compound #16)

Carbonic acid trans-6-ethoxy-8,8-diethyl-7-(1-phenyl-ethoxycarbonylamino)-5,6,7,8-tetrahydro-naphthalen-2-yl ester 1-phenyl-ethyl ester (less polar isomer) (31mg ; 0.055mmol) placed under nitrogen at room temperature was dissolved in dichloromethane (8.0mL) and trifluoroacetic acid (3.0mL) was then added and the reaction mixture was

stirred for about an hour. The solvents were then evaporated by vacuo and a solution of hydrochloric acid in ether (1.0M) (7mL) was then added. The reaction mixture thus obtained was then stirred for another hour. The solvents were removed by vacuo and the isolated solid washed several times with ether, hexanes, than dichloromethane. The isolated product is a yellow powder (15.7mg, 95%).

1H NMR (400MHz) (CD3OD; d; ppm): 6.98 (1H, d, J=8.9Hz, aromatic), 6.68 (2H, m, aromatics). 3.96 (1H, m, CH-NH2), 3.87 (1H, m), 3.56 (1H, m), 3.39 (2H, m), 2.57 (1H, dd, J1=10.0Hz, J2=15.5Hz), 2.07 (1H, m), 1.73 (1H, m), 1.66 (2H, m), 1.30 (3H, t, J=7.0Hz) 0.80 (3H, t, J=7.4Hz), 0.70 (3H, t, J=7.3Hz). [α]D +43.00° c = 0.2

step 2A

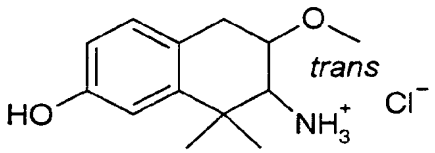
(+)Trans-3-Ethoxy-1,1-diethyl-7-hydroxy-1,2,3,4-tetrahydro-naphthalen-2-yl-ammonium chloride (compound #16)

Carbonic acid trans-6-ethoxy-8,8-diethyl-7-(1-phenyl-ethoxycarbonylamino)-5,6,7,8-tetrahydro-naphthalen-2-yl ester 1-phenyl-ethyl ester (more polar isomer) (32mg ; 0.057mmol) placed under nitrogen at room temperature was dissolved in dichloromethane (5.0mL) and trifluoroacetic acid (3.0mL) was then added and the reaction mixture was stirred for about an hour. The solvents were then evaporated by vacuo and a solution of hydrochloric acid in ether (1.0M) (10mL) was then added. The reaction mixture thus obtained was then stirred for another hour. The solvents were removed by vacuo and the isolated solid washed several times with pentane, hexanes, than dichloromethane. The isolated product is a yellow powder (10.3mg, 60%).

1H NMR (400MHz) (CD3OD; d; ppm): 6.98 (1H, d, J=8.9Hz, aromatic), 6.68 (2H, m). 3.96 (1H, m), 3.87 (1H, m), 3.56 (1H, m), 3.39 (2H, m), 2.57 (1H, dd, J1=10.0Hz, J2=15.5Hz), 2.07 (1H, m, CH2), 1.73 (1H, m), 1.66 (2H, m), 1.30 (3H, t, J=7.0Hz) 0.80 (3H, t, J=7.4Hz), 0.70 (3H, t, J=7.3Hz). [α]D -43.68° c = 0.19

In a like manner, the following compounds were prepared:

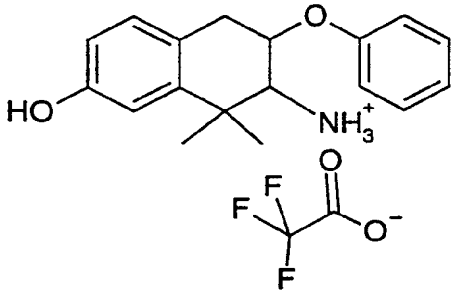
compound #2 (±)-TRANS-7-AMINO-6-METHOXY-8,8-DIMETHYL-5,6,7,8-TETRAHYDRO-NAPHTHALEN-2-OL HCL SALT



1H NMR (400MHz) (DMSO-d6; d; ppm): 9.24 (1H, bs), 8.30 (3H, bs), 6.88 (1H, d, J=9.3Hz), 6.74 (1H, d, J=2.2Hz), 6.59 (1H, dd, J=2.2 and 9.3Hz), 3.65 (1H, m), 3.43 (3H, s), 3.40 (1H, m), 3.27 (1H, m), 3.13 (1H, m), 1.40 (3H, s), 1.17 (3H, s).

compound #3

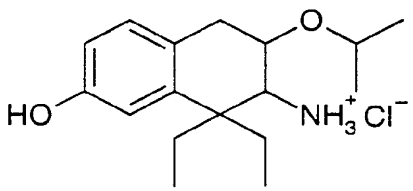
(±)-TRANS-7-AMINO-8,8-DIMETHYL-6-PHENOXY-5,6,7,8-TETRAHYDRO-NAPHTHALEN-2-OL TFA SALT



1H NMR (400MHz) (DMSO-d6; d; ppm): 9.26 (1H, bs), 8.31 (3H, bs), 7.34 (2H, t, J=8.5Hz), 7.15 (2H, d, J=8.1Hz), 7.01 (1H, t, J=7.2Hz), 6.88 (1H, d, J=8.4Hz), 6.78 (1H, d, J=2.4Hz), 6.60 (1H, dd, J=2.4 and 8.4Hz), 4.74(1H,m), 3.51 (1H, m), 3.30 (1H, dd, J=5.4 and 10.3Hz), 2.72 (1H, dd, J=5.4 and 10.3Hz), 1.47 (3H, s), 1.24 (3H, s).

compound #4

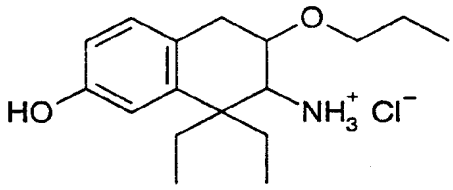
1,1-DIETHYL-7-HYDROXY-TRANS-3-ISOPROPOXY-1,2,3,4-TETRAHYDRO-NAPHTHALEN-2-YL-AMMONIUM CHLORIDE



1H NMR (400MHz) (CD3OD; d; ppm): 6.98 (1H, d, J=9.0Hz), 6.67 (2H, m). 4.04 (1H, m), 3.97 (1H, m), 3.34 (1H, m), 3.32 (1H, m), 2.58 (1H, dd, J1=10.0Hz, J2=15.6Hz), 2.05 (1H, m), 1.76 (1H, m), 1.68 (2H, dd, J1=7.5Hz, J2=15.1Hz), 1.28 (3H, d, J=6.1Hz), 1.25 (3H, d, J=6.0Hz), 0.79 (3H, t, J=7.5Hz), 0.69 (3H, t, J=7.2Hz).

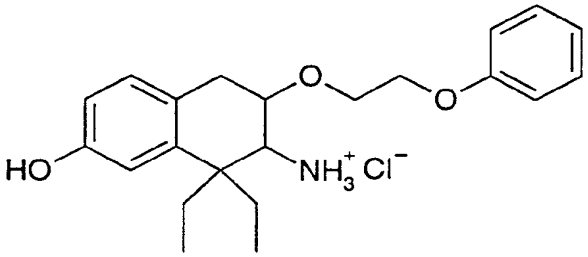
compound #5

(±) 1,1-DIETHYL-7-HYDROXY-TRANS-3-PROPOXY-1,2,3,4-TETRAHYDRO-NAPHTHALEN-2-YL-AMMONIUM CHLORIDE



1H NMR (400MHz) (CD3OD; d; ppm): 6.97 (1H, d, J=8.7Hz), 6.66 (2H, m). 3.94 (1H, m), 3.72 (1H, m), 3.48 (1H, dd, J1=7.0Hz , J2=14.1Hz), 3.39 (1H, m), 3.37 (1H, m), 2.55 (1H, dd, J1=9.8Hz, J2=15.3Hz), 2.06 (1H, m), 1.67 (5H, m), 1.00 (3H, t, J=7.3Hz), 0.78 (3H, t, J=7.3Hz), 0.68 (3H, t, J=7.0Hz).

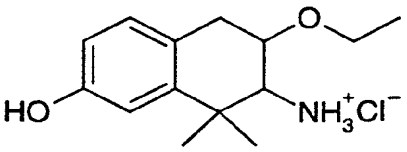
compound #6 (±)1,1-DIETHYL-7-HYDROXY-TRANS-3-(2-PHENOXY-ETHOXY)-1,2,3,4-TETRAHYDRO-NAPHTHALEN-2-YL-AMMONIUM CHLORIDE



1H NMR (400MHz) (CD3OD; d; ppm): 7.29 (2H, m), 6.96 (4H, m), 6.69 (2H, m), 4.23 (2H, m), 4.13 (2H, m), 3.93 (1H, m), 3.45 (2H, m), 2.64 (1H, dd, J1=9.9Hz, J2=15.5Hz), 2.07 (1H, m), 1.72 (1H, m), 1.67 (2H, m), 0.80 (3H, t, J=7.5Hz), 0.70 (3H, t, J=7.2Hz).

(±)compound #7

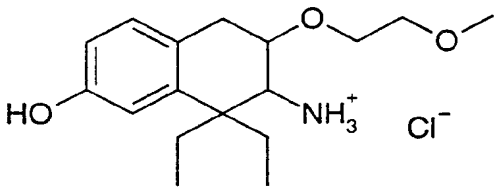
7-AMINO-TRANS-6-ETHOXY-8,8-DIMETHYL-5,6,7,8-TETRAHYDRO-NAPHTHALEN-2-OL HCL SALT



1H NMR (400MHz) (CD3OD; d; ppm): 6.94 (1H, d, J=8.3Hz), 6.79 (1H, d, J=2.4Hz). 6.64 (1H, dd, J1=2.4 Hz, J2=8.3Hz), 3.87 (1H, m), 3.77 (1H, m), 3.56 (1H, m), 3.35 (1H, m), 3.23 (1H, dd, J1=0Hz, J2=10.8Hz), 2.63 (1H, dd, J1=10.4Hz, J2=15.3Hz), 1.49 (3H, s), 1.31 (3H, t, J=7.0Hz), 1.28 (3H, s).

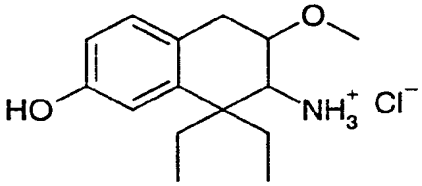
compound #8

(±)1,1-DIETHYL-7-HYDROXY-TRANS-3-(2-METHOXY-ETHOXY)-1,2,3,4-TETRAHYDRO-NAPHTHALEN-2-YL-AMMONIUM CHLORIDE



1H NMR (400MHz) (DMSO-d6; d; ppm): 9.24 (1H, bs), 7.97 (3H, bs), 6.91 (1H, d, J=8.2Hz), 6.60 (2H, m), 3.89 (1H, m), 3.79 (1H, m), 3.66 (1H, m), 3.54 (2H, m), 3.45 (2H, m), 3.28 (3H, s), 3.20 (1H, m), 1.84 (2H, m), 1.35 (2H,m), 0.66 (3H, t, J=7.3Hz), 0.56 (3H, t, J=7.1Hz).

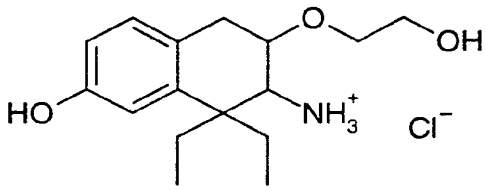
compound #9 (±)1,1-DIETHYL-7-HYDROXY-TRANS-3-METHOXY-1,2,3,4-TETRAHYDRO-NAPHTHALEN-2-YL-AMMONIUM CHLORIDE



1H NMR (400MHz) (CD3OD; d; ppm): 7.00 (1H, d, J=6,4Hz), 6.68 (2H, m). 3.87 (1H, m), 3.53 (3H, s), 3.41 (2H, m), 2.54 (1H, dd, J1=10Hz, J2=16Hz), 2.07 (1H, m), 1.71 (1H, m), 1.66 (2H, m), 0.80 (3H, t, J=7.5H), 0.70 (3H, t, J=7.3Hz).

compound #10

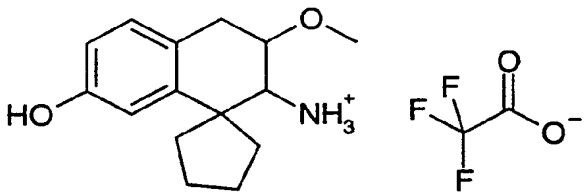
(±)1,1-DIETHYL-7-HYDROXY-TRANS-3-(2-HYDROXY-ETHOXY)-1,2,3,4-TETRAHYDRO-NAPHTHALEN-2-YL-AMMONIUM CHLORIDE



1H NMR (400MHz) (DMSO-d6; d; ppm): 9.22 (1H, bs), 7.96 (3H, bs), 6.91 (1H, d, J=8.2Hz), 6.60 (2H, m), 4.70 (1H,bs), 3.89 (1H, m), 3.79 (1H, m), 3.66 (1H, m), 3.54 (2H, m), 3.45 (2H, m), 3.20 (1H, m), 1.83 (2H, m), 1.58 (2H,m), 0.66 (3H, t, J=7.3Hz), 0.57 (3H, t, J=7.1Hz).

compound #11

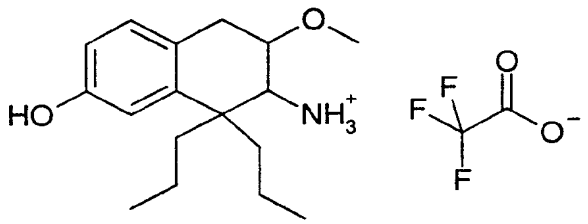
(±)-1,1-spiropentanyl trans-7-hydroxy-3-methoxy-1,2,3,4-tetrahydro-naphthalen-2-yl-ammonium; trifluoro-acetate



1H NMR (MeOD) : 6.95 (1H, d, J=8.5 Hz), 6.73 (1H, d, J=2.5 Hz), 6.63 (1H, dd, J=2.5 Hz and 8.5 Hz), 3.66 (1H, m), 3.53 (3H, s), 3.45-3.35 (2H, m), 2.65 (1H, dd, J=10 Hz and 16 Hz), 2.20 (1H, m), 2.15-1.95 (5H, m), 1.80-1.65 (2H,m).

compound #12

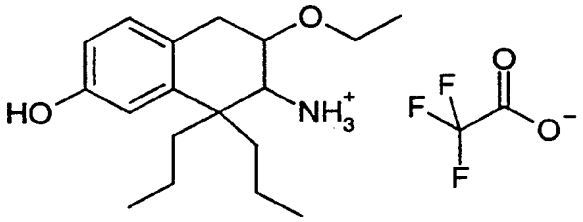
(±)7-Hydroxy-3-methoxy-1,1-dipropyl-1,2,3,4-tetrahydro-naphthalen-2-yl-ammonium; trifluoro-acetate



1H NMR (MeOD) : 6.99 (1H, d, J=8.0 Hz), 6.70-6.65 (2H, m), 3.84 (1H, qd, J=6.0 hz and 10.0 Hz), 3.53 (3H. s), 3.45-3.35 (2H, m), 2.54 (1H, dd, J=10.0 Hz and 15.5 Hz), 1.95 (1H, m), 1.73 (1H, m), 1.65-1.45 (2H, m), 1.30-1.05 (3H, m), 0.95-0.90 (4H, m), 0.86 (3H, t, J=7.0 Hz).

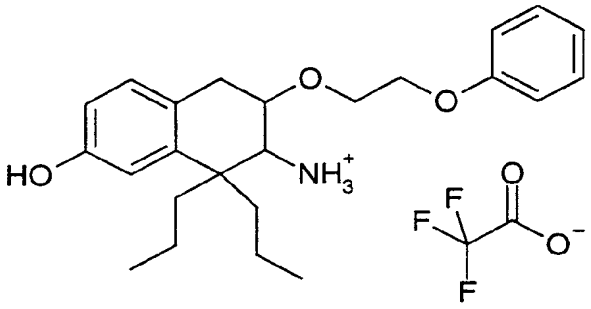
compound #13

(±)3-Ethoxy-7-hydroxy-1,1-dipropyl-1,2,3,4-tetrahydro-naphthalen-2-yl-ammonium; trifluoro-acetate



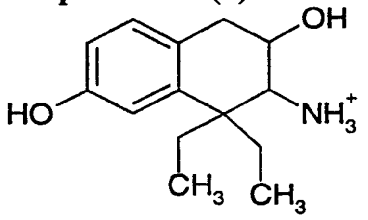
1H NMR (MeOD) : 6.98 (1H, d, J=8.0 Hz), 6.70-6.65 (2H, m), 4.00-3.85 (2H, m), 3.57 (1H. m), 3.39 (2H, m), 2.57 (1H, dd, J=10.0 Hz and 15.5 Hz), 1.95 (1H, m), 1.77 (1H, m), 1.65-1.50 (2H, m), 1.31 (3H, t, J=7.0 Hz), 1.30-1.05 (3H, m), 0.95-0.90 (4H, m), 0.86 (3H, t, J=7.0 Hz).

compound #14 (±)7-Hydroxy-3-(2-phenoxy-ethoxy)-1,1-dipropyl-1,2,3,4-tetrahydro-naphthalen-2-yl-ammonium; trifluoro-acetate



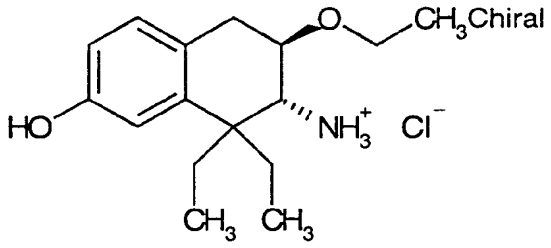
1H NMR (MeOD) : 7.31 (2H, t, J=8.0 Hz), 7.05-6.95 (4H, m), 6.70-6.65 (2H, m), 4.25 (2H, t, J=5.0 Hz), 4.20-4.05 (2H, m), 3.95 (1H. m), 3.50-3.45 (2H, m), 2.64 (1H, dd, J=10.0 Hz and 15.5 Hz), 1.95 (1H, m), 1.80-1.50 (3H, m), 1.30-1.05 (4H, m), 0.95-0.90 (4H, m), 0.86 (3H, t, J=7.0 Hz).

compound #15 (±) TRANS



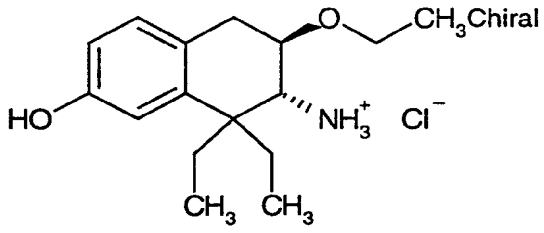
compound #16

(-)Trans-3-Ethoxy-1,1-diethyl-7-hydroxy-1,2,3,4-tetrahydro-naphthalen-2-yl-ammonium chloride



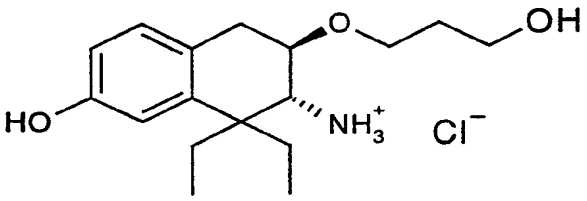
compound#17

(+)Trans-3-Ethoxy-1,1-diethyl-7-hydroxy-1,2,3,4-tetrahydro-naphthalen-2-yl-ammonium chloride



compound #18

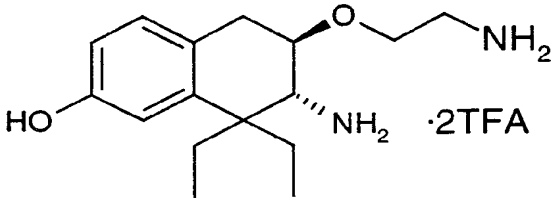
1,1-diethyl-7-hydroxy-3-trans-(3-hydroxy-propoxy)-1,2,3,4-tetrahydro-naphthalen-2-yl-ammonium; chloride



NMR (^{1}H, DMSO): 9.22(bs, 1H), 7.96 (s, 3H), 6.91(m,1H), 6.59 (m, 2H), 4.65 (m, 1 H), 4.00-3.00 (m, 8H), 2.10-1.70 (m, 4H), 1.54 (m, 2H), 0.66 (t, J = 7.2 Hz, 3H), 0.57 (t, J = 6.9 Hz, 3H).

compound #19

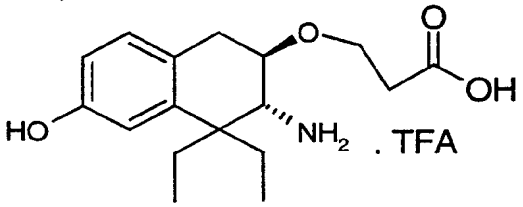
7-Amino-6-(2-amino-ethoxy)-8,8-diethyl-5,6,7,8-tetrahydro-naphthalen-2- ol; BIS-trifluoroacetic acid salt



^{1}H NMR (DMSO) : 9.28 (1H, s), 7.91 (3H,broad), 7.80 (3H, broad), 6.93 (1H, d, J=8.5 Hz), 6.64 (2H, m), 4.00-3.90 (2H, m), 3.60 (1H, m), 3.30 (2H, m), 3.20-3.05 (2H, m), 1.92 (1H, m), 1.84 (1H, m), 1.61 (2H, m), 0.69 (3H, t, J=7.5 Hz), 0.59 (3H, t, J=7.5 Hz).

compound #20

3-(3-Amino-4,4-diethyl-6-hydroxy-1,2,3,4-tetrahydro-naphthalen-2-yloxy)-propionic acid; trifluoroacetic acid salt



NMR (^{1}H, DMSO): 9.25 (bs, 1H), 7.87 (s, 3H), 6.93 (m,1H), 6.60 (m, 2H), 3.90 (m, 2 H), 3.71 (m, 2H), 3.30(m, 1H), 3.20 (m, 1H), 2.60 (m, 2H), 2.48 (m, 1H), 1.88 (m, 1H), 1.77 (m, 1H), 1.54 (m, 2H), 0.67 (t, J = 7.2 Hz, 3H), 0.58 (t, J = 6.9 Hz, 3H).

BIOLOGICAL ASSAYS

A. Receptor Affinity - Radioligand Binding Assay

Affinity for μ and δ opioid receptors was assessed in vitro using radioligand binding assay employing rat brain membrane preparations as described in Schiller et al., Biophys. Res. Commun., 85, p.1322 (1975) incorporated herein by reference. Male Sprague-Dawley rats weighing between 350-450g were sacrificed by inhalation of CO2. The rats were decapitated and the brains minus cerebellum were removed and place in ice-cold saline solution and then homogenized in ice-cold 50 mM Tris buffer pH 7.4 (10ml/brain). The membranes were centrifuged at 14000 rpm for 30 min. at 4°C. The pellets were re-suspended in approximately 6ml/brain of ice-cold Tris buffer 50mM pH 7.4 and stored at -78°C until ready for use. Protein quantification of the brain homogenate was conducted according to protein assay kit purchased (Bio-Rad).

(3H)- DAMGO and (3H) DAGLE were used as radioligands for the μ and δ receptors, respectively. Radioligand 50 μl, membranes 100 μl and serially diluted test compound were incubated for 1 hr at 22°C. Non specific binding was determined using 500 fold excess of unlabeled ligand in the presence of tracer and membranes. Free ligand was separated from bound by filtration through Whatman GF/B paper (presoaked in polyethylenimine 1% aqueous solution) and rinsing with ice-cold 50mM Tris pH 7.4 using a Brandel cell harvester. The filters were dried and radioactivity was counted in a 24 well microplate in the presence of 500 ml scintillant per well. Radioactivity was measured using a Wallac 1450 Microbeta counter. Inhibition constants (Ki) for the various compounds were determined from the IC50 according to the Cheng and Prusoff equation.

B. Central and Peripheral Analgesia - PBQ Writhing Assay

PBQ (phenyl-p-benzoquinone) induced writhing in mice was used to assess both central and peripheral analgesia of compounds of the invention according to the experimental protocol described in Sigmund et al., Proc. Soc. Exp. Biol. Med., 95, p. 729(1957) which is incorporated herein by reference. The test was performed on CD #1 male mice weighing between 18 and 22g. The mice were weighed and marked and administered peritoneally with 0.3ml/20g by weight 0.02% solution of phenylbenzoquinone (PBQ) . The contortions which appeared during a 15 minute time period following the injection were counted and ED50 values (dose of compound which induced a 50% reduction in the number of writhes observed compared to the control) was calculated. The PBQ was injected at time intervals of 5, 20 or 60 minutes after subcutaneous or oral administration of the compound (or medium, or standard).

PBQ solution was prepared by dissolving 20mg of PBQ in 5ml ethanol 90% (sigma, reagent, alcohol). The dissolved PBQ was slowly added to 95ml of distilled water continuously shaken and preheated (not boiled). The PBQ solution was left 2 hours before use, and at all times, protected from light. A new solution was prepared every day for the test.

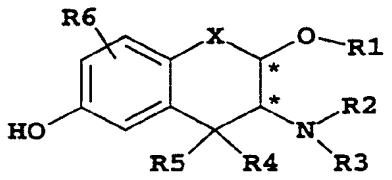
C. CENTRAL ANALGESIA TAIL FLICK ASSAY

The compounds of the present invention were evaluated for central analgesia as described in D'Amour et al. J.Pharmacol. 72:74-79, 1941 which is herein incorporated by reference.

While the invention has been described in connection with specific embodiments thereof, it will be understood that it is capable of further modifications and this application is intended to cover any variations, uses or adaptations of the invention following, in general, the principles of the invention and including such departures from the present description as come within known or customary practice within the art to which the invention pertains, and as may be applied to the essential features hereinbefore set forth, and as follows in the scope of the appended claims.

CLAIMS

1. A compound represented by formula (I)



(I)

and pharmaceutically acceptable derivatives thereof;

wherein;

X is selected from anyone of

(i) a bond;

(ii) $-CR_7R_8-$ wherein R_7 and R_8 are independently selected from the group consisting of H , OH, halogen, CN, COOH, $CONH_2$, amino, nitro, SH, C_{1-6} alkyl where one or more of the carbon atoms may optionally be substituted by one or more heteroatoms selected from O, S and N, C_{2-6}alkenyl where one or more of the carbon atoms may optionally be substituted by one or more heteroatoms selected from O, S and N, C_{2-6}alkynyl where one or more of the carbon atoms may optionally be substituted by one or more heteroatoms selected from O, S and N; and $COOR_c$ wherein R_c is C_{1-6}alkyl, C_{2-6}alkenyl or C_{2-6}alkynyl; R_7 and R_8 can also be connected to form C_{3-8} cycloalkyl, a C_{3-8} cycloalkenyl or a saturated heterocycle of from 3 to 8 atoms;

R_1 is selected from the group consisting of H, C_{1-12}alkyl where one or more of the carbon atoms may optionally be substituted by one or more heteroatoms selected from O, S and N, C_{2-12}alkenyl where one or more of the carbon atoms may optionally be substituted by one or more heteroatoms selected from O, S and N, C_{2-12}alkynyl where one or more of the carbon atoms may optionally be substituted by one or more heteroatoms selected from O, S and N, C_{6-12} aryl, C_{6-12} aralkyl, C_{6-12} aryloxy, C_{1-12} acyl, heteroaryl having from 6 to 12 atoms, and phosphoryl;

R_2 and R_3 are independently selected from the group consisting of C_{1-6} alkyl where one or more of the carbon atoms may optionally be substituted by one or more heteroatoms selected from O, S and N, C_{2-6}alkenyl where one or more of the carbon atoms may optionally be substituted by one or more heteroatoms selected from O, S and N, C_{2-6}alkynyl where one or more of the carbon atoms may optionally be substituted by one or more heteroatoms selected from O, S and N, C_{6-12} aryl, C_{6-12} aralkyl, heteroaryl having from 6 to 12 atoms, and H; ***or***

R_2 and R_3 may together form a saturated heterocycle of from 3 to 8 atoms;

R_4 and R_5 are independently selected from the group consisting of C_{1-6} alkyl where one or more of the carbon atoms may optionally be substituted by one or more heteroatoms selected from O, S and N, C_{2-6}alkenyl where one or more of the carbon atoms may optionally be substituted by one or more heteroatoms selected from O, S and N, C_{2-6}alkynyl where one or more of the carbon atoms may optionally be substituted by one or more heteroatoms selected from O, S and N, and H;

R_4 **and** R_5 can also be connected to form C_{3-8} cycloalkyl, a C_{3-8} cycloalkenyl or a saturated heterocycle of from 3 to 8 atoms;

R_6 is hydrogen, OH, C_{1-6} alkyl where one or more of the carbon atoms may optionally be substituted by one or more heteroatoms selected from O, S and N, C_{2-6}alkenyl where one or more of the carbon atoms may optionally be substituted by one or more heteroatoms selected from O, S and N, C_{2-6}alkynyl where one or more of the carbon atoms may optionally be substituted by one or more heteroatoms selected from O, S and N, O-C_{1-6} alkyl where one or more of the carbon atoms may optionally be substituted by one or more heteroatoms selected from O, S and N, O-C_{2-6}alkenyl where one or more of the carbon atoms may optionally be substituted by one or more heteroatoms selected from O, S and N, O-C_{2-6}alkynyl where one or more of the carbon atoms may optionally be substituted by one or more heteroatoms selected from O, S and N, halogen, CN, COOH, $CONH_2$, amino, nitro, or SH;

with the provisos that:

1) not both R_4 and R_5 are H; and

2) at least one of R_2 and R_3 is H or C_{1-6} alkyl.

2. The compound of claim 1 wherein **X** is -CH_2-.

3. The compound of claim 2 wherein the geometric relation between the substituents of carbons marked by an * is *trans*.

4. The compound of claim 3 wherein R_2 and R_3 are H.

5. The compound of claim 3 wherein R_6 is H.

6. The compound of claim 5 wherein R_4 and R_5 are C_{1-4} alkyl.

7. The compound of claim 5 wherein R_4 and R_5 are independently selected from the group consisting of methyl, ethyl, isopropyl, propyl, butyl, and isobutyl.

8. The compound of claim 5 wherein R_4 and R_5 are ethyl.

9. The compound of claim 5 wherein R_4 and R_5 are methyl.

10. The compound of claim 5 wherein R_1 is selected from the group consisting of H, C_{1-12}alkyl, C_{6-12} aryl, and C_{6-12} aralkyl.

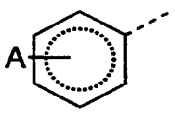
11. The compound of claim 5 wherein R_1 is selected from the group consisting of C_{1-6}alkyl, C_{6-12} aryl, and C_{6-12} aralkyl.

12. The compound of claim 5 wherein R_1 is C_{1-6} alkyl.

13. The compound of claim 5 wherein R_1 is selected from the group consisting of CH_3, $-(CH_2)_n-CH_3$, and $-(CH_2)_n-O-CH_3$ wherein n is an integer selected between 1 and 5.

14. The compound of claim 5 wherein R_1 is C_{6-12} aryl.

15. The compound of claim 14 wherein R_1 is selected from the group consisting of



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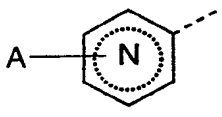
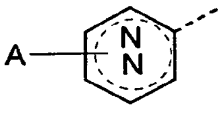
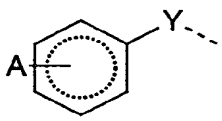


, and


wherein **A** is selected from the group consisting of C_{1-6} alkyl, C_{1-6}alkyl, C_{1-6}alkenyl, C_{1-6}alkynyl, O-C_{1-6} alkyl, O-C_{2-6}alkenyl, O-C_{2-6}alkynyl, , S-C_{1-6} alkyl, S-C_{2-6}alkenyl, S-C_{2-6}alkynyl, N-C_{1-6} alkyl, N-C_{2-6}alkenyl, N-C_{2-6}alkynyl, CF_3, fluoro, chloro, bromo, iodo, OH, SH, CN, nitro, amino, aminoamidino, amidino, guanido, COOH, and $COOR_z$ wherein R_z is C_{1-6}alkyl, C_{2-6}alkenyl or C_{2-6}alkynyl.

16. The compound of claim 5 wherein $\mathbf{R_1}$ is C_{6-12} aralkyl.

17. The compound of claim 16 wherein $\mathbf{R_1}$ is selected from the group consisting of



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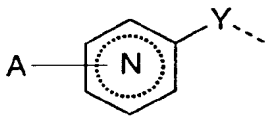
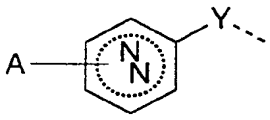


, and


wherein **A** is selected from the group consisting of C_{1-6} alkyl, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, O-C_{1-6} alkyl, O-C_{2-6}alkenyl, O-C_{2-6}alkynyl, , S-C_{1-6} alkyl, S-C_{2-6}alkenyl, S-C_{2-6}alkynyl, N-C_{2-6} alkyl, N-C_{2-6}alkenyl, N-C_{2-6}alkynyl, CF_3, fluoro, chloro, bromo, iodo, OH, SH, CN, nitro, amino, aminoamidino, amidino, guanido, COOH, and $COOR_z$ wherein R_z is C_{1-6}alkyl, C_{2-6}alkenyl or C_{2-6}alkynyl and **Y** is $-(CH_2)_m-$ wherein **m** is an integer selected between 1 and 5.

18. The compound of claim 1 wherein said compound selected from the group consisting of

Trans-7-Amino-6-ethoxy-8,8-diethyl-5,6,7,8-tetrahydro-naphthalen-2-ol (**compound#1**);

Trans-7-Amino-6-methoxy-8,8-dimethyl-5,6,7,8-tetrahydro-naphthalen-2-ol (**compound#2**);

Trans-7-Amino-8,8-dimethyl-6-phenoxy-5,6,7,8-tetrahydro-naphthalen-2-ol (**compound#3**) ;

Trans-7-Amino-6-isopropoxy-8,8-dimethyl-5,6,7,8-tetrahydro-naphthalen-2-ol **compound#4** ;

Trans-7-Amino-8,8-dimethyl-6-propoxy-5,6,7,8-tetrahydro-naphthalen-2-ol (**compound#5**) ;

Trans-7-Amino-8,8-dimethyl-6-(2-phenoxy-ethoxy)-5,6,7,8-tetrahydro-naphthalen-2-ol (**compound#6**) ;

Trans-7-Amino-6-ethoxy-8,8-dimethyl-5,6,7,8-tetrahydro-naphthalen-2-ol (**compound#7**) ;

Trans-7-Amino-8,8-diethyl-6-(2-methoxy-ethoxy)-5,6,7,8-tetrahydro-naphthalen-2-ol (**compound#8**) ;

Trans-7-Amino-8,8-diethyl-6-methoxy-5,6,7,8-tetrahydro-naphthalen-2-ol (**compound#9)** ;

Trans-7-Amino-8,8-diethyl-6-(2-hydroxy-ethoxy)-5,6,7,8-tetrahydro-naphthalen-2-ol (**compound#10)** ;

Trans-7-Amino-8,8-spiropentanyl-6-methoxy-5,6,7,8-tetrahydro-naphthalen-2-ol (**compound#11)** ;

Trans-7-Amino-6-methoxy-8,8-dipropyl-5,6,7,8-tetrahydro-naphthalen-2-ol **(compound#12)** ;

Trans-7-Amino-6-ethoxy-8,8-dipropyl-5,6,7,8-tetrahydro-naphthalen-2-ol **(compound#13)** ;

Trans-7-Amino-6-(2-phenoxy-ethoxy)-8,8-dipropyl-5,6,7,8-tetrahydro-naphthalen-2-ol **(compound#14)** ;

Trans-3-Amino-4,4-diethyl-1,2,3,4-tetrahydro-naphthalene-2,6-diol **(compound#15)** ;

(-)Trans-3-Ethoxy-1,1-diethyl-7-hydroxy-1,2,3,4-tetrahydro-naphthalen-2-yl-ammonium chloride **(compound #16)** ;

(+)Trans-3-Ethoxy-1,1-diethyl-7-hydroxy-1,2,3,4-tetrahydro-naphthalen-2-yl-ammonium chloride **(compound #17)** ;

1,1-diethyl-7-hydroxy-3-trans-(3-hydroxy-propoxy)-1,2,3,4-tetrahydro-naphthalen-2-yl-ammonium; chloride **(compound#18);**

7-Amino-6-(2-amino-ethoxy)-8,8-diethyl-5,6,7,8-tetrahydro-naphthalen-2- ol; BIS-trifluoroacetic acid salt **(compound#19);**

3-(3-Amino-4,4-diethyl-6-hydroxy-1,2,3,4-tetrahydro-naphthalen-2-yloxy)-propionic acid; trifluoroacetic acid salt **(compound#20);**

and pharmaceutically acceptable derivative thereof.

19. The compound of claim 18 wherein said compound selected from the group consisting of **compound#1, compound#2, compound#3, compound#4, compound#5, compound#6, compound#7, compound#8, compound#9, compound#12, compound#16, compound#17, compound#18 and compound#19.**

20. The compound of claim 19 wherein said compound selected from the group consisting of **compound#1, compound#2, compound#5, compound#8, compound#9, compound#16 and compound#17.**

21. The compound of claim 19 wherein said compound selected from the group consisting of **compound#16 and compound#17.**

22. A compound according to any one of claims 1 to 20 wherein said compound is in the form of the (+) enantiomer, the (-) enantiomer and mixture of the (+) and (-) enantiomer including racemic mixture.

23. A compound according to any one of claims 1 to 20 wherein said compound is in the form of the (+) enantiomer.

24. A compound according to any one of claims 1 to 20 wherein said compound is in the form of the (-) enantiomer.

25. A compound according to any one of claims 1 to 24 for use in therapy.

26. A method of treating pain in a mammal comprising administering to said mammal an analgesic amount of a compound as defined in any one of claims 1 to 24.

27. A pharmaceutical composition comprising a compound as defined in any one of claims 1 to 24 and pharmaceutically acceptable carriers, diluents or adjuvants.

28. Use of a compound according to anyone of claims 1-24, for the manufacture of a medicament for the treatment of pain.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 99/02402

A. CLASSIFICATION OF SUBJECT MATTER

IPC7: C07C 215/44, C07C 215/46, C07C 217/52, A61K 31/135, A61P 25/04
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC7: C07C, A61K, A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	GB 1377356 A (EISAI CO., LTD.), 11 December 1974 (11.12.74), page 2, line 37 - line 40 ---	1-28
X	EP 0378456 A1 (MERRELL DOW PHARMACEUTICALS INC.), 18 July 1990 (18.07.90), page 2, line 1 - line 15 ---	1-28
X	STN International, File CAPLUS, CAPLUS accession no. 1973:546294, Document no. 79:146294, Tanabe Seiyaku Co., Ltd: "1,1-Dimethyl-2-dimethylamino-7-hydroxy-1,2,3,4-tetrahydronaphtahalene"; & JP,A2,48057962,19730814, ---	1-28

[X] Further documents are listed in the continuation of Box C. [X] See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" erlier document but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
19 April 2000	26 -04- 2000
Name and mailing address of the ISA Swedish Patent Office Box 5055, S-102 42 STOCKHOLM Facsimile No. +46 8 666 02 86	Authorized officer Nebil Gecer/ELY Telephone No. +46 8 782 25 00

Form PCT/ISA 210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 99/02402

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	STN International; File CAPLUS, CAPLUS accession no. 1976:542882, Document no. 85:142882, Hirose, Noriyasu et al: "Synthesis and analgesic activities of some 2-amino-1,1-dialkyl-7-methoxy-1,2,3,4-tetrahydronaphthalenes and related compounds"; Yakugaku Zasshi (1976), 96(2), 185-94	1-28
	--	
X	Chemical Abstracts, Volume 84, No 7, 16 February 1976 (16.02.76), (Columbus, Ohio, USA), THE ABSTRACT No 43700e, JP, 7537764 A,, (Hirose, Noriyasu et al) 8 April 1975 (08.04.75)	1-28
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X	STN International, File CAPLUS, CAPLUS accession no. 1985:55638, Document no. 102:55638, Staneva, D. et al: "Parmacological study of 2-aminotetralin derivatives", Farmatsiya (Sofia) (1984), 34 (3), 15-19	1-28
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X	STN International, File CAPLUS, CAPLUS accession no. 1982:597950, Document no. 97:197950, Christova, K. et al: "Derivatives of 2-amino-1,2,3,4-tetrahydronaphthalene. VII. Aroyl esters" of cis- and trans-2-dimethylamino-3-hydroxy-5,8-dimethoxy.1,2,3,4-tetrahydronaphthalenes", Arch.Pharm.(Weinheim, Ger.) (1982), 315(9), 797-801	1-28
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X	STN International, File CAPLUS, CAPLUS accession no. 1978:182828, Document no. 88:182828, Rainova, L. et al: "Neuropharmacological profile of an aminotetralin derivative", Eksp.Med.Morfol. (1977), 16(4), 211-16	1-28
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INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 99/02402

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	STN International, File CAPLUS, CAPLUS accession no. 1978:6589, Document no. 88:6589, Dantchey, D. et al: "Derivatives of 2-amino-1,2,3,4-tetrahydronaphthalene. II. Synthesis and pharmacological investigation of N-substituted trans-2-amino-3-hydroxy-5,8-dimethoxy-1,2,3,4-tetrahydronaphthalenes", Arch.Pharm. (Weinheim, Ger.)(1977), 310(5), 369-79 --	1-28
A	US 4267373 A (FREDERIC PH. HAUCK ET AL), 12 May 1981 (12.05.81), claim 12 --	1-28

INTERNATIONAL SEARCH REPORT

International application No.
SE99/02402

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 26
because they relate to subject matter not required to be searched by this Authority, namely:

See extra sheet.

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).:

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.
SE99/02402

Claim 26 is directed to a method of treatment of the human or animal body by therapy methods practised on the human or animal body (see PCT, Rule 39.1 (iv)). Nevertheless, a search has been executed for this claim. The search has been based on the alleged effects of the compounds/compositions.

INTERNATIONAL SEARCH REPORT

Information on patent family members

02/12/99

International application No.
PCT/SE 99/02402

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
GB 1377356 A	11/12/74	CH 589600 A	15/07/77
		DE 2340629 A	21/03/74
		FR 2196158 A,B	15/03/74
		JP 49054353 A	27/05/74
		JP 51024508 B	24/07/76
EP 0378456 A1	18/07/90	SE 0378456 T3	
		AT 94533 T	15/10/93
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		AU 4782790 A	12/07/90
		CA 2007261 A	09/07/90
		CN 1022319 B	06/10/93
		CN 1044460 A	08/08/90
		DE 69003257 D,T	13/01/94
		DK 378456 T	25/10/93
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		JP 2233650 A	17/09/90
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		NZ 232031 A	28/07/92
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		US 5106861 A	21/04/92
JP 7537764 A	08/04/75	NONE	
US 4267373 A	12/05/81	CA 1017359 A	13/09/77
		DE 2333847 A	24/01/74
		FR 2190464 A,B	01/02/74
		JP 49051255 A	18/05/74
		US 3930022 A	30/12/75
		US 4076843 A	28/02/78